Rearrangement of 3-Alkyl-1-allylindoles: a Model Reaction for the Biogenesis of Echinulin-type Compounds [1]

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3-Alkyl-1-allylindoles (1) rearrange under acid catalysis to give the 2-substituted derivatives (2) and (3) with partial inversion of the migrating group (but-2-enyl, 3-methylbut-2-enyl). This represents a hitherto unobserved type of rearrangement, which may have both biogenetic and synthetic implications for echinulin-type compounds. The mechanism of the reaction has been proved to be intramolecular by a ' cross-over ' experiment with deuteriated specimens.

SEVERAL structurally similar compounds, *i.e.* echinulin,[2] neoechinulin,[3] brevianamides,[4-6] and austamides,[6,7] biogenetically derivable from tryptophan and mevalonic acid, have been isolated as mould metabolites. All formally present, among other fragments, a 1,1-dimethylallyl unit at position 2 of a tryptophan system.

Various attempts [8] to synthesize alkaloids of this type have been made and a laborious stereoselective total synthesis of echinulin has been successfully achieved.[9] Different hypotheses have been suggested concerning the mechanism of insertion of the reversed isoprene chain into the indole nucleus.[10] Studies carried out with model compounds tend to exclude both a direct S_N2' attack at C-2 [11] by the 3-methylbut-2-enyl pyrophosphate and a primary attack at C-3, followed by rearrangement.[12] Admittedly, the control is essentially enzymic, but little is known about the nature and the mode of action of the enzymes involved. Recently, Allen [13] has isolated the enzymic system which catalyses the transfer of the isoprene group from 3-methylbut-2-enyl pyrophosphate to cyclo-L-alanyl-L-tryptophanyl. His data seem to indicate a primary introduction of the reversed isoprene unit at the 2-position of such a system in the biogenesis of echinulin. However, we had postulated previously [1] that isoprenoid substitution takes place first on the nitrogen atom, followed by rearrangement to the 2-position. Our suggestion is now supported by the recent isolation of lanosulin [14] from cultures of *Penicillium lanosum*, which contains a 3-methylbut-2-enyl group at the 1-position of a complex tryptophan system. This metabolite might represent the missing biogenetic link for this group of compounds.

The paper describes our research on the reactivity of 3-alkyl-1-(3-methylbut-2-enyl)indoles as model systems for the biogenesis and the synthesis of echinulin-type compounds.

Substituted indoles are known to rearrange under acidic conditions to give more basic compounds: thus, 3-alkylindoles lead to 2-alkylindoles [15] and 2-acyl- to 3-acyl-indoles.[16] Accordingly, it seems possible to hypothesize a 1,2-rearrangement, with thermodynamic control (pK_a 1,3-dimethylindole = −3·3; pK_a 2,3-di-

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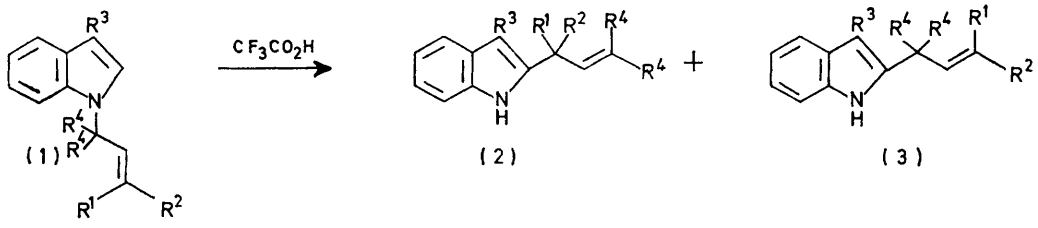
methylindole = −1·49).[17] Studies of the rearrangement with different acids [1] indicated trifluoroacetic acid (TFA) as the most suitable medium for such reactions. Thus, in TFA 3-methyl-1-(3-methylbut-2-enyl)indole (1c) rearranges to 2-(1,1-dimethylallyl)-3-methylindole (2c) and to 3-methyl-2-(3-methylbut-2-enyl)indole (3c). Reactions performed with compounds bearing differently substituted allyl chains (1a—c) indicated that the rates

Considerations on the mechanism of the reaction indicated that, presumably, protonation of the indole nucleus occurs first, leading to an intermediate which subsequently rearranges to the 2-substituted derivatives (2) and (3). Therefore, studies on the position of protonation of 3-alkyl-1-allylindoles in TFA seemed advisable. N.m.r. spectra showed that protonation of 3-methyl-1-(3-methylbut-2-enyl)indole had occurred at



	R^1	R^2	R^3	R^4
a;	H	H	Me	H
b;	H	Me	Me	H
c;	Me	Me	Me	H
d;	Me	Me	Pr^n	H
e;	Me	Me	Bu^t	H
f;	Me	Me	$[^2H_2]Me$	^2H

of rearrangement increase markedly in the order: allyl ≪ but-2-enyl < 3-methylbut-2-enyl. On the other hand, the ratio between the rearranged derivatives (2) : (3) increases in the order 3-methylbut-2-enyl < but-2-enyl and when the reaction is performed at lower temperature (see Table 1).

TABLE 1

Rearrangement of 3-alkyl-1-allylindoles in CF_3CO_2H *

Substrate	Amount recovered (%)	Yield of products (%) (2)	(3)	Unidentified products (%)	Ratio (2) : (3)
(1a)	100			*a*	
(1b)	36	36	14	14	72 : 28
(1c)	*a*	50	50	*a*	50 : 50
(1c) [b]	*c*	32	68	*a*	32 : 68
(1c) [d]	*c*	65	35	*a*	65 : 35
(1d)	3	45	52	*a*	46 : 54
(1e)	20		10	70	0 : 100

* At room temperature for 48 h, unless stated otherwise.

[a] Trace quantities. [b] At reflux for 1 h. [c] Unchanged products were unestimated. [d] At 0° for 7 days.

The same rearrangement was observed with 1-(3-methylbut-2-enyl)-3-n-propylindole (1d). In contrast, with a substrate bearing a bulkier 3-substituent (3-t-butyl) (1e), only the 2-(3-methylbut-2-enyl) derivative (3e) was obtained in low yield. The rest of the mixture, examined by u.v. and n.m.r., contained unidentified indole compounds with saturated substituents. It is conceivable that steric [18] factors as well as an eventual loss of the t-butyl group [19] may considerably alter the reaction course.

the 3-position, to give the 3*H*-indolium salt, as previously evidenced for other indole substrates.[17,20] Unfortunately, quantitative determinations were impossible to achieve, since the spectrum was complicated by overlapping signals due to protonated rearrangement products. Studies with 1-allyl-3-methylindole in TFA confirmed a high extent of 3-protonation (99%). Thus, the 3-methyl resonance is shifted to high field ($\Delta\delta$ = 0·50 p.p.m.), whereas the signals due to the *N*-methylene and to the 2-indole proton experience a downfield shift ($\Delta\delta$ = 0·71 and 2·40 p.p.m., respectively). Furthermore, a new signal at δ 4·51 (3-H) [20b] is present. Therefore, a 3-protonated species seems to be the most probable intermediate for this new type of rearrangement.

Tests were made to check whether the rearrangement occurs with an inter- or intra-molecular mechanism. For this purpose, 1-(3-methylbut-2-enyl)-3-n-propylindole was allowed to rearrange in the presence of 3-methylindole, which being only partially protonated in TFA [20b] can act as trapping agent for electrophilic systems. No traces of the possible 'cross-over' products were observed, in so far as 3-methylindole gave only dimerization products.[21] Furthermore, no intermolecular products were obtained from the simultaneous rearrangement of 1-(3-methylbut-2-enyl)-3-n-propylindole and 1-(but-2-enyl)-3-methylindole. Finally, the intramolecularity of the process was definitely established by employing isotopic techniques. A 'cross-over' reaction was carried out with (1c) and the corresponding tetradeuteriated specimen 3-$[^2H_2]$methyl-1-(3-methyl[1-$^2H_2$]but-2-enyl)indole (1f). The possibility

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that an intermolecular process had occurred was ruled out by the absence of dideuterated specimens ($M + 2$) in the mixture of the rearranged products (2) + (3), examined by accurate mass measurements. The relative ion intensity data are reported in Table 2. Tracer experiments on the possibility that the 1,2-rearrangement may occur *in vivo* are in progress.

TABLE 2

Relative ion intensity data for the rearranged products

Rearranged products from	[M]	[$M + 2$]	[$M + 4$]
(1c)	100	1·5	
(1f)	3	6·5	100
(1c) + (1f)	100	6·9 * (6·6)	79

* Average of three different values. Theoretical value in brackets.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord 137 instrument. U.v. spectra were determined on a Beckman DK-2 spectrophotometer for 95% ethanol solutions. N.m.r. spectra were recorded on a C-60-HL JEOL instrument for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard. Mass spectra were obtained with a Hitachi–Perkin-Elmer model RMW-6-D instrument at 70 eV. G.l.c. was performed with a Varian Aerograph, model 1400, with a flame ionization detector; a 150 cm × 1/8 in stainless steel column (5% SE-30 on 60—80 silanized Chromosorb W) was used. Quantitative determinations were made isothermally at 150°, using 3-n-propylindole as internal standard. Preparative g.l.c. was performed with a Varian Aerograph, model 90 P3; a 100 cm × 1/4 in stainless steel column (20% SE-30 on 60—80 silanized Chromosorb W) at 150° was used. Kieselgel 60 (70—230 mesh) Merck was used for column chromatography. T.l.c. was performed on Merck PF_{254} silica gel. Preparative t.l.c. was carried out on layers 1 mm thick.

Preparation of 3-Alkyl-1-allylindoles (1a—f).—A 3-alkylindole (0·5 mol) in anhydrous dimethylformamide (DMF) (25 ml) and allyl bromide (0·075 mol) in DMF (25 ml) were added in turn to a suspension of NaH (0·075 mol) in DMF (25 ml) and the mixture stirred for 3 h at room temperature. The complex was decomposed with water and the product extracted with ether. On removal of the solvent, a residue was obtained which was purified by column chromatography (hexane as eluant). Analytical data for the products are reported in Table 3, and spectral data in Table 4.

TABLE 3

Analytical data for 3-alkyl-1-(3-methylbut-2-enyl)indoles and their corresponding hydrogenated * rearrangement products

	Found (%)				Required (%)		
Compd.†	C	H	N	Formula	C	H	N
(1b)	84·25	8·2	7·3	$C_{13}H_{15}N$	83·1	8·7	7·4
(1c)	83·85	8·8	6·85	$C_{14}H_{17}N$	84·35	8·6	7·05
(1d)	84·75	9·5	6·1	$C_{16}H_{21}N$	84·55	9·55	6·05
(1e)	84·85	9·7	5·55	$C_{17}H_{23}N$	84·6	9·6	5·8
(2′b)	83·6	9·2	7·35	$C_{13}H_{17}N$	83·35	9·15	7·5
(3′b)	92·95	9·0	7·25	$C_{13}H_{17}N$	83·35	9·15	7·5
(2′c)	83·4	9·4	6·85	$C_{14}H_{19}N$	83·55	9·5	6·95
(3′c)	83·05	9·3	6·6	$C_{14}H_{19}N$	83·55	9·5	6·95
(2′d)	83·95	10·2	6·0	$C_{16}H_{23}N$	83·8	10·1	6·1
(3′d)	83·3	9·9	5·85	$C_{16}H_{23}N$	83·8	10·1	6·1
(3′e)			5·5	$C_{17}H_{25}N$			5·75

* Indicated by primed numbers. † Compound (1a) is known (ref. 12).

Rearrangement of 3-Alkyl-1-allylindoles with Trifluoroacetic Acid.—A solution of the 3-alkyl-1-allylindole (500 mg) in trifluoroacetic acid (40 ml) was magnetically stirred under nitrogen at the temperatures and for the reaction times previously described (Table 1). The mixture was neutralized with sodium hydrogen carbonate and extracted with ether. Quantitative analyses (g.l.c.) were performed under the conditions described before and products corresponding up to the 95 (±5%) of the starting material were detected. The rearranged isomers (2) + (3) were separated from the mixture by preparative t.l.c. (hexane–ethyl

TABLE 4

Spectral data for 3-alkyl-1-(3-methylbut-2-enyl)indoles

	U.v.[b]	N.m.r.[c] δ ($CDCl_3$) [d]			
Compound	$\lambda_{max.}$ (log ε)/nm	Indole-2-H	CH=	N–CH_2	CH_3 [e]
(1b)	228 (4·48), 288 (3·78)	6·80br, s	5·3—5·6, m	4·3—4·5, m	1·5—1·8, m
(1c)	228 (4·51), 292 (3·74)	6·75, q ($J_{CH_3,2-H}$ 1 Hz)	5·27br, t	4·46, d ($J_{CH_2,CH}$ 7 Hz)	1·69br, s
(1d)	228 (4·47), 292 (3·85)	6·80br, s	5·35, t	4·61, d ($J_{CH_2,CH}$ 7 Hz)	1·75br, s
(1e)	228 (4·45), 291 (3·77)	6·80, s	5·35, t	4·62, d ($J_{CH_2,CH}$ 7·5 Hz)	1·80br, s

[a] I.r. N–H stretching absent. [b] In 95% EtOH. [c] Only significant signals are reported. [d] Integrations fit the assignments. [e] These resonances refer to methyl groups in 1-substituent.

TABLE 5

N.m.r. data of the allyl chains in the rearranged products (2) and (3)

	δ ($CDCl_3$) [a]				
Compound	CH=	$=CH_2$	Ar·CH	Ar·CH_2	CH_3
(2b)	5·7—6·4 (8 lines)	5·8 and 5·12, dt	3·5—4·0, m		1·41, d [b]
(3b)	5·4—5·7, m			3·3—3·5, m	1·4—1·8, m
(2c) [c]	6·07, dd	5·10 and 5·09, dd [d]			1·48, s
(3c) [c]	5·07, t			3·38, d [e]	1·73br, s

[a] Integrations fit the assignments. [b] J_{CH,CH^3} 7; J_{cis} 10; J_{trans} 17; $J_{gem} \simeq J_{all} \simeq 1$ Hz. [c] Similar results were obtained for the products from the rearrangement of (1d) and (1e). [d] J_{cis} 10, J_{trans} 17, J_{gem} 1 Hz. [e] $J_{CH_2,CH}$ 7 Hz.

acetate, 9 : 1) under nitrogen. I.r. spectra showed the presence of the NH stretching at 3400 cm^{-1}; u.v. spectra were consistent with an indole structure; $\lambda_{max.}$ 228 (log ε 4·5), 285 (3·8), 291 (3·7) nm. No evidence for the signal at δ 6·8 (2-H of indole) was found in the n.m.r. spectra, whereas signals corresponding to the aromatic protons, to the NH proton, and to the 3-substituent were in agreement with the structures expected. The chemical shifts of the signals corresponding to the allyl chains are reported in Table 5.

The relative percentages of the rearranged products (2) and (3) were calculated from the ratios of the discrete signals in the n.m.r. spectra. Quantitative g.l.c. analyses for compounds (2c), (2d), (3c), and (3d) were also possible after preparative g.l.c. and identification of the products by i.r. spectra. However, quantitative g.l.c. analyses of the whole mixture obtained by rearrangement of (1b—e) were possible only after hydrogenation (PtO_2, 1 atm). Only in this way could products (1), (2), and (3) be separated.

The analytical data for the hydrogenated rearrangement products (2′) and (3′) isolated by preparative g.l.c. are reported in Table 3.

3-([$^2H_2$]methyl)indole was prepared by reduction of indole-3-carbaldehyde with $LiAlD_4$ according to a known procedure.[22]

3-Methyl[1-$^2H_2$]but-2-enyl bromide was prepared by reduction of dimethylacrylic acid with $LiAlD_4$ [23] and subsequent reaction with PBr_3.[24]

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